Abstract

Cellular prion protein (PrP^C) is a glycosylphosphatidylinositol-anchored glycoprotein present on the outside leaflet of the cellular membrane of the most cell types in mammals. Despite the fact that PrP^C is highly conserved among species, its physiological function has not been fully clarified yet. Defining the function of PrP^C remains one of the main challenges in prion biology. The development of transmissible spongioform encephalopathies (TSE) is associated with the conversion of PrP^C into the misfolded, pathogenic isoform called, scrapie isoform (PrP^{Sc}). Special class among TSEs represents inherited diseases, where spontaneous conversion to PrP^{Sc} is generated by mutation in gene coding for PrP. Approximately 10-15% of all TSEs are associated with the mutations wordwide. The important debate in prion biology involves identification of the regions that lead to the favoured conversion process on the structural level of PrP^C, whereby alpha-helical motifs are replaced by beta-sheet secondary structures that are prone to form amyloid fibrils.

The content of this work is focused on nuclear magnetic resonance (NMR) solution-state structure determination of the PrP^C, carrying the pathological point mutation linked to genetic type of TSEs. NMR spectroscopy is a powerful tool providing information on three-dimensional structural features at the atomic level. We undertook solution-state studies of huPrPs with pathological Q212 and V210I mutations linked to Gerstmann-Sträussler-Scheinker (GSS) syndrome and genetic Creutzfeldt–Jakob disease (CJD), respectively and huPrP carrying naturally occurring E219K polymorphism, considered to protect against sporadic CJD (sCJD). We believe that observed structural features of investigated mutants are a step forward towards establishing a structure-function relationship which provides a biological basis for understanding the spontaneous generation of PrP^{Sc} in inherited prion diseases.